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My name and post office address are as stated below:

That I am knowledgeable in the English language and in the Japanese language, and that I believe the English translation attached is a true and complete translation of JP 10226650 to Masanobu et al.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

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[Title of The Invention]

Glycyrrhizin preparations for oral administration

[Claims]

[Claim 1]

An oral preparation of glycyrrhizin characterized in that at least one principal drug selected from the group consisting of glycyrrhizin and a salt thereof, and an absorption promoter are solubilized in a solubilizing agent, and the solubilized product is coated with an enteric coating film.

[Claim 2]

The oral preparation of claim 1 wherein, as said absorption promoter, at least either one of a middle-chain fatty acid or a salt thereof is contained.

[Claim 3]

The oral preparation of claim 2 wherein said absorption promoter is capric acid or a salt thereof.

[Detailed Description of The Invention]

[0001]

[Technical Field]

The present invention relates to an oral preparation having enhanced transfer of glycyrrhizin or its salt into blood.

[0002]

[Prior Art and Problems]

Glycyrrhizin, a derivative or salt thereof is known to have, when used alone or in combination with amino acids, a variety of pharmacological activities such as anti-cortisone activity, de-chlesterol activity, anti-infalmmatory activity, anti-allergic activity, detoxicating activity, anti-stomach ulcer activity and so on. Recently, the efficacy of intravenous administration of a large dose of glycyrrhizin or its salt for the treatment of chronic hepatitis has been reported. Therefore, glycyrrhizin preparations are mainly used for the treatment of hepatic disease as injection preparations. Since hepatic disease generally requires a long term, daily administration of a drug, I.V. administration of a glycyrrhizin preparation not only gives pain to the patient but causes hypertrophy in the tissue of injected site by a long term daily administration.

[0003]

Consequently, the best way to solve these problems would be to formulate glycyrrhizin in an oral preparation. However, oral glycyrrhizin preparations of systematic action now in the market have been reported to have a problem of decreased transfer rate into the blood due to the enzymatic decomposition in the digestive tract and the metabolism during the first

pass through the liver. Moreover, the decomposition product produced in the digestive tract by enzyme has possibility of inducing a side-effect such as pseudoaldosteronism. Thus oral glycyrrhizin preparations now in the market include many problems.

[0004]

Therefore, many studies have been conducted to develop a pharmaceutical preparation of glycyrrhizin other than injections which can transfer glycyrrhizin into the blood without enzymatic degradation in the digestive tract. For example, the rectal suppositories have been reported for replacement of oral preparations.

(1) Because glycyrrhizin is absorbed from the rectum and then transferred into the blood, a rectal suppository has been reported. See, JP-A-03002122.

(2) It has been reported that the blood transfer of glycyrrhizin is promoted by rectal administration of a dispersion of glycyrrhizin in a lipophilic base (such as Witepsol or Migriol). See, JP-A-03123731.

(3) It has been reported that a rectal suppository exhibiting excellent absorbability is obtained by combining glycyrrhizin and at least either an absorption-promoting nonionic surfactant (such as

polyoxyethylene lauryl ether) or a middle-chain fatty acid salt (such as alkali metal salt of capric acid or capronic acid). See, JP-A-04261117.

[0005]

(4) It has been reported that a rectal suppository exhibiting excellent absorbability is obtained by combining glycyrrhizin, an absorption promoting nonionic surfactant (such as polyoxyethylene alkyl ether) and optionally a water-soluble carboxylic acid (such as malonic acid or capric acid) or a salt thereof. See, JP-A-05097680.

(5) It has been reported that a rectal suppository exhibiting excellent absorbability is obtained by combining glycyrrhizin and an absorption promoter (such as sodium caprate) and a pH adjusting agent (such as sodium hydroxide) or ursodeoxycholic acid. See, JP-A-07082155.

[0006]

However, many patients appeal discomfort in long term administration of the rectal suppository although the number is fewer than injections. So, oral preparations are still desired for long term administration. Therefore, the following studies have been reported to produce an oral preparation of glycyrrhizin.

(6) It has been reported that an oral preparation exhibiting excellent absorbability is obtained by combining glycyrrhizin and a fatty acid glyceride (such as mono-, di- or triglyceride of stearic acid or capric acid), and then providing an enteric film thereon. See, JP-A-03255037.

(7) It has been reported that an oral preparation exhibiting excellent absorbability at the upper part of small intestine is obtained by combining a lipid emulsion or lipid complex mixture of glycyrrhizin and an absorption promoter (such as nonionic surfactant, middle-chain fatty acid, a salt or glyceride thereof) to produce dry powder, and then shaping the powder followed by coating the shaped product with an enteric film. See, JP-A-06192107. These preparations, however, do not exhibit sufficient absorbability into the body compared to the blood level of injection preparations having well-established efficacy.

[0008]

[Means For Solving Problems]

The present inventors have studied the formulation method of glycyrrhizin to improve its absorption into the body upon oral administration. As a result, they have discovered that an oral preparation exhibiting very excellent absorbability in comparison

with prior art preparations may be obtained by combining glycyrrhizin or a salt thereof, a middle-chain fatty acid or salt thereof or both as an absorption promoter, and optionally a pH adjusting agent, then solubilizing the mixture in a solubilizing agent, and coating the resulting product with an enteric film. Namely, it has been discovered that very excellent absorption in comparison with prior art preparations may be achieved by allowing delivery of the principal ingredient to lower part of the digestive tract (particularly in the large intestine) in a solubilized state of the principal ingredient and the absorption promoter.

[0009]

The absorption-promoting effect of the middle-chain fatty acid and a salt thereof is reported to be maximum generally in the large intestine. For example, see, Development of Medicaments, Drug Delivery Method, 13, 50-71 (1988). A drug delivery method to the large intestine has been developed. See, JP-A-03007718. However, only a very small amount of water is present in the large intestine because the large intestine is the water-absorbing site and, therefore, a sufficient quantity of water is not provided unlike the upper part of digestive tract.

Consequently, delivery of a drug and an absorption promoter to the large intestine in solid state was not effective to improve the absorption sufficiently. The present invention has solved this problem by solubilizing the solid drug and absorption promoter in a solubilizing agent.

[0010]

Solubilization of glycyrrhizin and absorption promoter has been thought very difficult as is apparent from the above-cited prior art (7) wherein a lipid emulsion or a complex mixture in lipid is used. The inventors have succeed the solubilization using the solubilizing agent of the present invention. Namely, the inventors achieved for the first time to prepare an oral preparation by solubilizing glycyrrhizin and a middle-chain fatty acid or a salt thereof acting as absorption promoter by the solubilizing agent of the present invention.

[0011]

[Construction of The Invention]

The present invention relates to (1) an oral preparation of glycyrrhizin characterized in that at least one principal drug selected from the group consisting of glycyrrhizin and a salt thereof, and an absorption promoter are solubilized in a solubilizing

agent, and the solubilized product is coated with an enteric coating film. It also relates to the oral preparation of glycyrrhizin of (1) wherein, as said absorption promoter, at least either one of a middle-chain fatty acid or a salt thereof is contained. It further relates to the oral glycyrrhizin preparation of (2) wherein said absorption promoter is capric acid or a salt thereof.

[0012]

As the principal drug of the preparation of the present invention, any pharmaceutically acceptable salt of glycyrrhizin may be used. Examples thereof include alkaline metal salt (potassium and sodium), alkaline earth metal salts (calcium and magnesium), ammonium salt, and pharmaceutically acceptable organic amine salts (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl) aminomethane, lysine, arguinine, N-methyl-D-glucamine). Glycyrrhizin disodium salt, glycyrrhizin dipotassium salt or glycyrrhizin monoammonium salts are particularly preferred. These salts may be used alone or in combination.

[0013]

As the absorption promoter of the preparation of the invention, a middle-chain fatty acid and a salt are mentioned. Examples thereof include capric acid, caprylic acid, caproic acid, alkali metal salts thereof (potassium and sodium), and alkaline earth metal salts thereof (calcium and magnesium). Capric acid and sodium caprate are particularly preferred.

[0014]

As the solubilizing agent of the preparation of the present invention, polyethylene glycol such as PEG 400, propylene glycol, nonionic surfactants such as hydrogenated castor oil HCO-60, and distilled water are mentioned. These are used alone or in combination. A combination of PEG 400, propylene glycol and distilled water or a combination of PEG 400 and distilled water is particularly preferred.

[0015]

The ratio of glycyrrhizin to the absorption promoter may vary depending on the particular promoter used and lies as molar ratio preferably between 20:1 and 1:20, more preferably between 8:1 and 1:8.

[0016]

As the preferable solubilizing agent, a combination of PEG 400, propylene glycol and distilled

water contains these ingredients in weight ratio preferably from 6:1:1 to 1:1:1, more preferably from 4:1:1 to 3:1:1. In case of the combination of PEG 400 and distilled water, a weight ratio is preferably from 6:1 to 1:1, more preferably from 4:1 to 3:1.

[0017]

The proportions of glycyrrhizin, capric acid or a salt thereof, PEG 400, propylene glycol, distilled water, and sodium hydroxide as the pH adjusting agent are as follows:

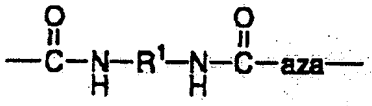
Glycyrrhizin	5 - 30 wt.%
Capric acid or its salt	5 - 30 wt. %
PEG 400	20 - 50 wt.%
Propylene glycol	0 - 10 wt.%
Distilled water	0 - 10 wt.%
Sodium hydroxide	0 - 3 wt.%
Total	100 wt.%

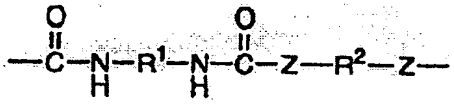
[0018]

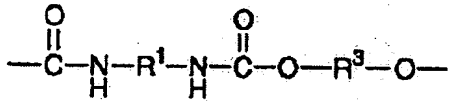
As the pH adjusting agent, alkali metal hydroxides (potassium and sodium) or alkaline earth metal hydroxides (calcium and magnesium) are preferable. Sodium hydroxide is particularly preferable.

[0019]

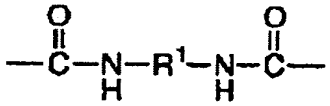
As the material of enteric film of the preparation of the present invention, those conventionally used in pharmaceutical preparations may be used. For example, carboxymethylethylcellulose, hydroxypropylmethyl-cellulose phthalate, cellulose acetate, methacrylic acid copolymers and azo polymers may be used. Generally known azo polymers may be used. For example, azo polymers disclosed in JP-A-0300718 may be used. Preferable azo polymers have an average MW from 1000 to 100,000 and consist of segments of

A-B: 

A-C: 

A-D: 

wherein A, B, C and D represent

A: 

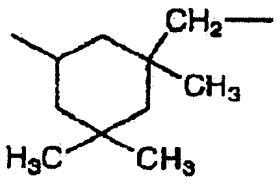
B: —aza—

C: $Z-R^2-Z$

D: $-O-R^3-O-$

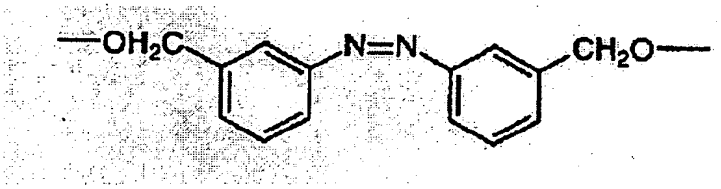
wherein the molar ratio x:y:z of segments A-B, A-C and A-D is 0.01-0.8:0-0.80:0:99 (x+y+z=1.0).

In the above formulas, R^1 represents in A-B, A-C and A-D a group of the formula (1):



(1)

azo represents the group of the formula (2):



(2)

Z-R^2-Z represents the residue of polyethylene glycol; and

R^3 represents 1,2-propylene bridge.

Preferable azo polymers are those described in Example 12 and Example 12(a) of JP-A-03007718.

[0024]

The preferred form of the oral preparation of the present invention is capsule preparations. Soft capsule preparations are more preferable. If necessary, the preparation may contain stabilizers, surfactants, diluents, additives, lubricants, auxiliary solubilizers,

preservatives and so on. The glycyrrhizin content is not limited to a particular amount provided that the preparation contains glycyrrhizin in an amount sufficient to exhibit its pharmacological effect. The dose may vary depending on the condition and age of the patient and is from 1 to 500 mg in a single dose. This dose may be administered once a day or several times per day.

[0025]

[Advantage]

The preparation of the present invention comprises glycyrrhizin or a salt thereof and a middle-chain fatty acid or a salt thereof as absorption promoter solubilized in a solubilizing agent, and an enteric coating film applied thereon. When orally administered, the preparation is delivered to the lower part of digestive tract (particularly large intestine). This enables glycyrrhizin to be absorbed into the body at a high concentration. Also, the oral administration can achieve a sufficient pharmacological effect comparable to intravenous administration.

[0026]

The invention will now be explained in detail by making reference to the following Production Examples and Examples but the invention is not limited thereto.

All parts therein are by weight.

[0027]

Production Example 1: Solution Formulation

According to the following formulation, polyethylene glycol and propylene glycol were mixed. To the mixture was added gradually glycyrrhizin ammonium salt with kneading. Then, sodium caprate powder was added with stirring to obtain a clear solution.

[0028]

[Table 1]

Ingredients	Parts
Glycyrrhizin ammonium salt	30
Sodium caprate	12
Propylene glycol	5
Polyethylene glycol 400	53
Total	100

[0029]

Production Example 2: Solution Formulation

According to the following formulation, polyethylene glycol and propyleneglycol were mixed. To the mixture was gradually added glycyrrhizin dipotassium salt with kneading. Then sodium caprate powder was added with stirring to obtain a clear

solution.

[0030]

[Table 2]

Ingredients	Parts
Glycyrrhizin dipotassium salt	30
Sodium caprate	12
Propylene glycol	5
Polyethylene glycol 400	53
Total	100

[0031]

Production Example 3: Solution Formulation

According to the following formulation, polyethylene glycol and propyleneglycol was mixed. To the mixture was added gradually glycyrrhizin disodium salt with kneading. The sodium caprate powder was added with stirring to obtain a clear solution.

[0032]

[Table 3]

Ingredients	Parts
Glycyrrhizin disodium salt	30
Sodium caprate	12
Propylene glycol	10
Polyethylene glycol 400	48
Total	100

[0033]

Production Example 4: Solution Formulation

According to the following formulation, polyethylene glycol was added to an aqueous solution of sodium hydroxide. To the solution was added glycyrrhizin ammonium salt with kneading and then molten capric acid with stirring to obtain a clear solution.

[0034]

[Table 4]

Ingredients	Parts
Glycyrrhizin ammonium salt	30
Capric acid	15
Water	8.8
Sodium hydroxide	1.2
Polyethylene glycol 400	45
Total	100

[0035]

Production Example 5: Solution Formulation

According to the following formulation, polyethylene glycol was added to an aqueous solution of sodium hydroxide. To the solution was added glycyrrhizin ammonium salt with kneading and molten

capric acid with stirring to obtain a clear solution.

[0036]

[Table 5]

Ingredients	Parts
Glycyrrhizin ammonium salt	20
Capric acid	25
Water	8.3
Sodium hydroxide	1.7
Polyethylene glycol 400	45
Total	100

[0037]

Production Example 6: Solution Formulation

According to the following formulation, polyethylene glycol was added to an aqueous solution of sodium hydroxide. To the solution were added glycyrrhizin ammonium salt with kneading and capric acid with stirring to obtain a clear solution.

[0038]

[Table 6]

Ingredients	Parts
Glycyrrhizin ammonium salt	15
Cabric acid	30
Water	7.7
Sodium hydroxide	2.3

Polyethylene glycol 400	45
Total	100

[0039]

Production Example 7-1: Oral Preparation of Solution Formulation

The solution of Production Example 1 was processed into a soft capsule preparation for oral administration containing about 45 mg of glycyrrhizin disodium salt/capsule.

[0040]

Production Examples 7-2 to 7-6: Oral Preparation of Solution Formulation

Production Example 7-1 was followed using solutions of Production Examples 2-6 to produce an oral preparation.

[0041]

Production Example 8-1:Oral Preparation of Solution Formulation With Enteric Coating

Soft capsule preparation of Production Example 7-1 was coated with 10 % of carboxylmethylethyl-cellulose in a spray pan coating machine to produce an oral preparation.

[0042]

Production Examples 8-2 to 8-6: Oral Preparation

of Solution Formulation With Enteric Coating

Production Example 8-1 was followed using soft capsule preparations of Production Examples 7-2 to 7-6 to produce oral preparations.

[0043]

Production Example 9-1: Oral Preparation of Solution Formulation With Enteric Coating

Soft capsule preparation of Production Example 7-1 was coated with 15 % of carboxymethylethyl-Cellulose in a spray pan coating machine to produce an oral preparation.

[0044]

Production Examples 9-2 to 9-6: Oral Preparation of Solution Formulation With Enteric Coating

Production Example 9-1 was followed using soft capsule preparations of Production Examples 7-2 to 7-6 to produce oral preparations.

[0045]

Production Example 10-1: Oral Preparation of Solution Formulation With Enteric Coating

Soft capsule preparation of Production Example 7-1 was coated 5 % azo polymer (Example 12 of JP-A-03007718) in a spray pan coating machine to produce an oral preparation.

[0046]

Production Examples 10-2 to 10-6: Oral Preparation of Solution Formulation With Enteric Coating

Production Example 10-1 was followed using soft capsule preparations of Production Examples 7-2 to 7-6 to produce oral preparations.

[0047]

Comparative Example 1: Oral Preparation of Powder Formulation

Using Noparel core (purified sugar particles of 24-34 mesh), powders of the following formulation were pelletized into granules of about 1 mm diameter in a centrifugal fluid bed pelletizer to produce an oral preparation containing 39.4 % of glycyrrhizin disodium salt and 17 % of sodium caprate.

[0048]

[Table 7]

Ingredients	Parts
Glycyrrhizin disodium salt	53
Sodium caprate	25
Low-substitution hydroxypropylcelluse (L-HPC)	15
Microcrystalline cellulose	7
Total	100

[0049]

Comparative Example 2: Oral Preparation of Powder Formulation With Enteric Coating

The oral preparation of Comparative Example 1 was coated with 10 % of carboxymethylethyl-Cellulose and 7 % of azo polymer (Example 12 of JP-A-03007718) to produce an oral preparation.

[0050]

Test Example1

Oral preparations of Production Examples 7-1, 8-1, 9-1, Comparative Examples 1 and 2 were respectively administered p.o. to beagle dogs at a dose of 50 mg/kg as glycyrrhizin disodium. Blood samples were collected from the forearm over time. Plasma glycyrrhizin levels were measured by HPLC and AUC (mg. min./1ml) from 0 to 8 hours was calculated. This value was compared with AUC of dogs given glycyrrhizin i.v. at a dose of 2 mg/kg as glycyrrhizin disodium to calculate bioavalability. The results are shown in Table 8.

In a separate test, the oral preparation of Production Example 10-1 (50 mg/kg) and commercially available glycyrrhizin tablets (100 mg/kg) were administered to separate groups of beagle dogs (n=2-6) and plasma glycyrrhizin levels (mean value + S.D.)

over time were determined. The results are shown in Fig. 1

[0051]

[Table 8]

	Route	Dose	AUC	Bioavailability
Aqueous Solution	I.V.	2mg/kg	3408.0	100 %
Commercial tab.	P.O.	100mg/kg	310.2	0.2 %
Comp.Ex.1	P.O.	50mg/kg	653.4	0.8 %
Comp.Ex.2	P.O.	50mg/kg	1202.0	1.4 %
Ex.7-1	P.O.	50mg/kg	2012.0	2.4 %
Ex.8-1	P.O.	50mg/kg	3378.0	4.0 %
Ex.9-1	P.O.	50mg/kg	4656.2	5.5 %
Ex.10-1	P.O.	50mg/kg	5140.5	6.0 %

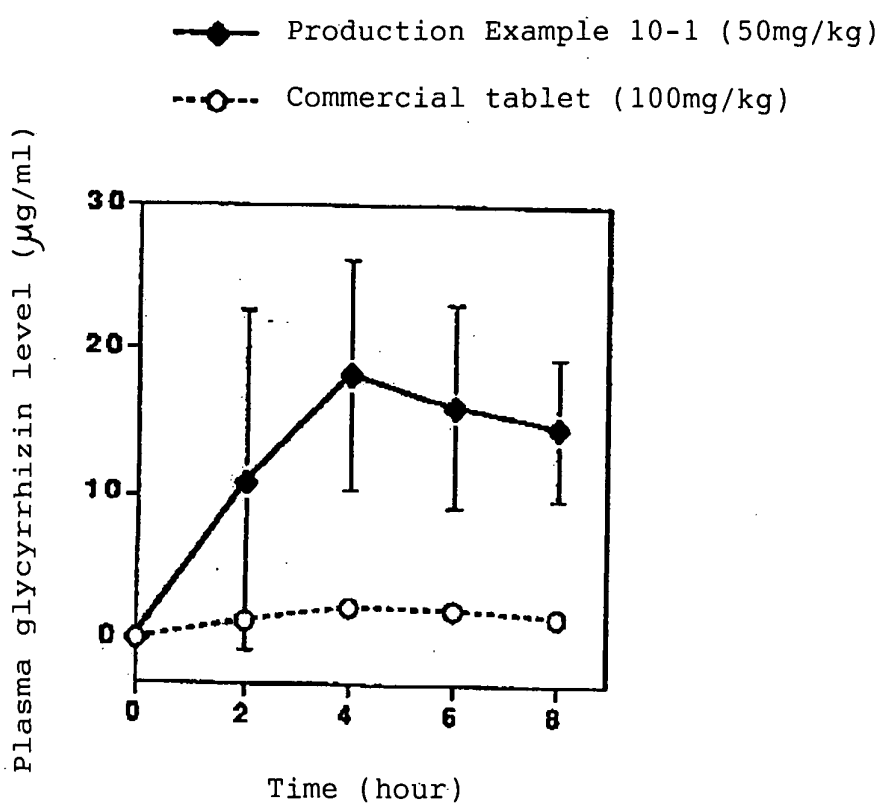
[0052] Observation

The above results demonstrate that the oral preparation of the present invention exhibited very excellent absorption over commercially available tablets, the oral preparation of powder formulation (Comparative Example 1), and the oral preparation of powder formulation with enteric coating (Comparative Example 2). Therefore, it becomes possible to improve the absorption of orally administered glycyrrhizin and its salt into the body.

[Brief Description of the Drawing]

Fig. 1. shows plasma glycyrrhizin levels the oral preparation of Production Example 10-1 over time in comparison with commercial tablets.

Fig. 1


Production Example 10-1 (50mg/kg)
Commercial tablet (100mg/kg)
Plasma glycyrrhizin level (μg/ml)
30
20
10
0
0
2
4
6
8
Time (hour)